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Combined Surgery and Photodynamic Therapy of Cancer

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Invited Paper

Abstract

According to the recent guidelines, the gold standard is resecting an extra 0.5-3 cm beyond the lesion margins that are visually detected and/or biopsy confirmed depending on type of malignancy and its localisation to avoid missing the residuals of the tumour. Often, such a large resection leads to dysfunctions of the organ or tissues, which underwent the surgery. In some cases, an extra tumour-free margin cannot be achieved because of tumour proximity to vital sites such as major vascular or nerve structures. Photodynamic Therapy (PDT) is an emerging clinical modality to locally destroy cancer lesions selectively. The limitation of photodynamic therapy is the curable depth of an order of one centimetre or less. A combination of cancer surgery following by PDT can bring a benefit to reduce the resection and minimise the impact on the organ or tissue functionality. Combination of cancer surgery and photodynamic therapy provides another opportunity – fluorescence image guidance of cancer removal. Most of the photosensitizers intensively fluoresce and hence facilitate a strong fluorescence contrast versus healthy adjacent tissues.

Keywords: cancer; surgery; photodynamic therapy; PDT; fluorescence; imaging

1. Cancer Surgery Guidelines

Surgery, in fact, remains the primary modality of treatment for malignancies, and standard resection is the only therapy required for early-stage cancer. As the stage of the tumor increases in terms of depth of penetration and lymph node involvement, the chance of cure with surgery alone diminishes. Rates of local recurrence and survival are dependent on the tumor–node–metastasis (TNM) stage[1,2,3,4]. The current review is limited to non-invasive cancer cure. The recent guidelines imply resecting an extra 0.5-3 cm beyond the lesion margins that are visually detected and/or biopsy confirmed depending on type of malignancy and its localisation to avoid missing the residuals of the tumour (so called prophylactic extended tumor resection as a protective barrier against intraoperative tumor cell traversal into severed lymphatics and vessels).[5] Often, such a large resection leads to dysfunctions of the organ or tissues, which underwent the surgery.[6] In some cases, an extra tumor-free margin cannot be achieved because of tumor proximity to vital sites such as major vascular or nerve structures.[7] In general case, the cancer surgery is guided by both surgeon estimation of cancer lesion margin profile and histology post processing.

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The guidance can be improved by a selective method of cancer destruction.
One of the selective approaches is Photodynamic Therapy, a method which is based on selective uptake of active photochemical catalyser called photosensitizer in malignant tumours. One of the mechanisms of selective uptake of photosensitizer within malignant tumour is associated with pharmacokinetic retention of the photochemical compounds due to cancer angiogenesis peculiarities – growth of premature leaky blood vessels in cancer lesions.

2. Photodynamic Therapy of Cancer

Photodynamic Therapy (PDT) is a non-surgical treatment modality based on photochemical reactions. PDT is extremely precise and controllable targeting malignant lesions. PDT is time effective as a procedure (e.g. a large malignancy can be exposed to laser light at once), and it does not develop a resistance demonstrating a very low mutagenic potential as DNA is usually not targeted and there is no opportunity for treatment induced mutation. PDT is particularly important for certain superficial clinical applications such as destroying a large lesion of cancer *in situ* in hollow organs like esophagus or lungs. The interaction of laser radiation with biological matter depends on various factors like respectively power density, wavelength, interaction time and material properties (e.g. absorption, scattering). The physical processes involved in the interaction of laser beam and material are divided into three parts: (1) absorption of some of the light energy; (2) transformation of this energy into chemical energy and/or into heat; (3) eventually, chemical reaction and/or phase transformation. The PDT domain is marked on the graph representing the photobiological effects depending on the fluence rate and the interaction time duration proposed by Boulnois in 1986.[8]

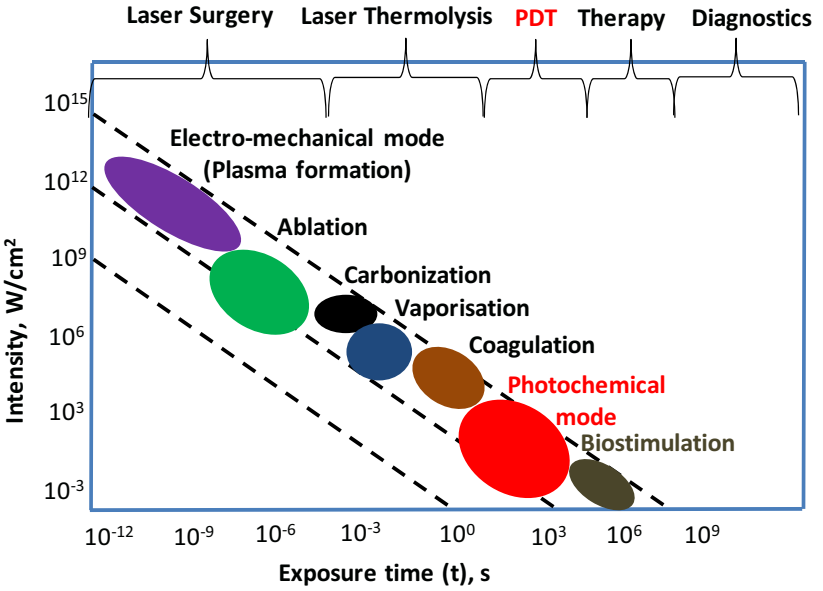

Fig. 1. Laser tissue interaction effects depending on power density and interaction time. The PDT domain is shown red. (Modified from[8]).

As it can be seen from Fig. 1, PDT does not require large dose of light energy and usually neither ablation nor hyperthermal effects are significant. PDT recently implied as a photochemical reaction involving light, photosensitive molecules absorbing light or photosensitizer (PS) and ambient molecular oxygen (O_2) to generate reactive oxygen species (ROS) which in turn destroy biotissue.[9] These include the Type I (sensitizer-substrate) and Type II (sensitizer-oxygen) reactions. Type I photochemical reactions result in the formation of superoxide anions by transfer of an electron from the photosensitizer to molecular oxygen. Superoxide anions can react to produce

hydrogen peroxide (H_2O_2), which can easily pass through biological membranes and produce cellular damage. Type II photochemical reactions represent the transfer of energy to molecular oxygen. During type II photochemical reaction, singlet oxygen ($^1O_2$) is generated. On a molecular level, the PDT initiates lipid peroxidation, a chain degenerative process that affects cell and intracellular membranes and the lipid containing structures under conditions of oxidative stress.[10] Membrane lipids may be a central site of photodamage if sensitizing agents localize in the membrane bilayer.[11] Another mechanism by which cells might be damaged during the photodynamic therapy is via the covalent crosslinking of proteins to proteins or to other molecules in the cell.[12] The lipid peroxidation and protein cross-linking may ultimately lead to necrosis and apoptosis. The diagram of cell fate pathways after PDT depending on the severity of damage[13] is presented in Fig. 2.

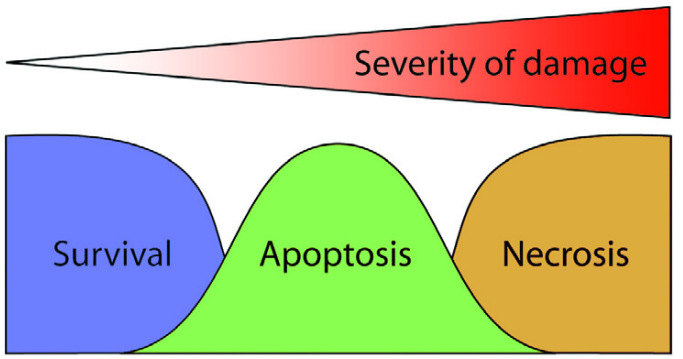

Fig. 2. Diagram of cell fate pathways after PDT depending on the severance of damage. (Modified from [14]).

If light cannot reach the photosensitizer, it cannot cause the necessary reaction that kills the cancer. Therefore, it only works in places in the body that light can reach, such as the skin and the lining of internal organs. Limitations of PDT include delay of treatment effect for hours or days after the session and shallow depth of treatment (~ 1 cm) due to limited penetration of light in biological tissues. In case of bulk tumors, PDT provides destruction of only superficial layer of the tumor.

3. Combined Surgery and Photodynamic Therapy of Cancer

Yet in 1998 it was firstly reported that PDT combined with surgery (tumor bed sterilization) gave significant local control of the primary tumor and significant reduction in distant metastases. By contrast, both treatment alone (surgery or PDT) gave relatively poorer local control, and PDT gave a significant increase in the mean number of lung metastases. [18] A combined therapeutic approach of stenting and photodynamic therapy was found leading to significant reductions in mortality rates in the year following treatment, compared with stenting treatment alone for advanced liver bile duct cancer.[15] Stenting can help reinforce the bile duct to increase liver functionality, the light therapy assisted in attacking the cancer cells directly. Lung surgery can be successfully combined with PDT. If surgery was used to remove cancer from the lungs, then photodynamic therapy could be used on top of that to keep it from coming back in places like the pleura, or lining of the lung.[16] Surgery of colorectal tumors was combined with PDT in an attempt to kill any microscopic tumor cells that may remain after surgical removal of the tumor. PDT was performed at the time of surgery, or after surgery to a perineal tumor.[17] Concluding, a combination of surgery, to clean the tumor bed within the obvious delineation, along with following PDT to selectively destroy the peripheral, not obviously delineated part of the lesion, enhances the overall efficacy of the cancer removal.[18]

4. Clinical Control of Combined Surgery and Photodynamic Therapy of Cancer

Combination of cancer surgery and photodynamic therapy provides another opportunity – image guidance of cancer removal. Most of the photosensitizers intensively fluoresce and hence facilitate a strong fluorescence contrast versus healthy adjacent tissues.[19,20] Usage of fluorescence large field imaging facility provides convenient real time navigation. Two fluorescence imaging guiding options can be used. Autofluorescence of normal tissue is much higher than that of the cancer.[21] An example of image guided surgery is shown in Fig. 3.[22]

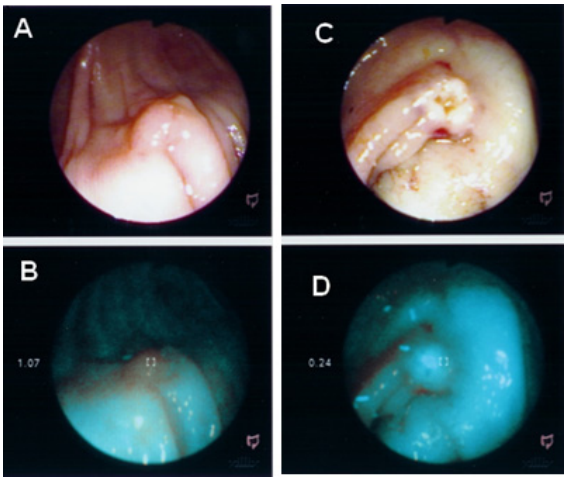

Fig. 3. Autofluorescence navigated surgery in colon (B, D) versus conventional white light mode (A,C). Left (A,B): adenomas polyp before resection; Right (C,D): after resection, no residual dysplasia left.

Left upper (which is white light) and lower (autofluorescence mode) pictures are presenting the diagnostics and lesion margin delineation of adenomas polyp before the resection. In the fluorescence mode the lesion looks like a reddish spot on a background of healthy gloving surrounding providing a crisp contrast.

In some organs such as stomach or esophagus, this technique does not really help because of too high false positive rate and the lack of specificity.[23] However, a selective uptake of the photosensitizer in tumor can be used facilitating the contrast between normal and malignant tissues. A surgery under control of malignant tumor contrast with PDT photosensitizer ALA-5 is shown in Fig. 4.[24] Both techniques can be combined.[25]

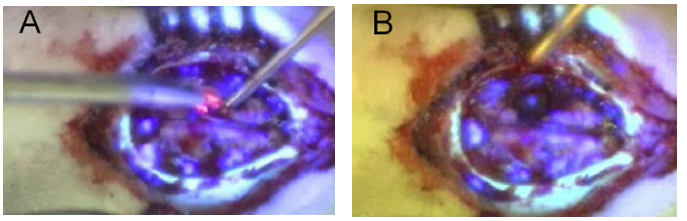

Fig. 4. Fluorescence navigated surgery in rat brain using ALA-5 photosensitizer. A - red fluorescence spot (between the tools) is cancer tumor. B – post fluorescence guided resection, no residual fluorescence left. (Courtesy of A. Bogaarts, 2005).

Concluding, the image guided surgery and therapy are expected to be more efficient and reducing the tumor re-occurrence probability as compare to non-guided modalities.

5. Future Trends and Conclusions

The general trend of development of contemporary clinical modalities in cancer treatment is directed towards “smart and aggressive” technologies. “Smart” means treatment integrated with diagnostics within the same facility and the term “aggressive” implies combination of several tumour eradicating strategies for higher efficacy. Combined surgery and photodynamic therapy of cancer along with the advanced imaging control are all aligned with the general trend.

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